PATIENT PACKAGE INSERT IN ACCORDANCE WITH THE PHARMACISTS' REGULATIONS (PREPARATIONS) - 1986

The medicine is dispensed with a doctor's prescription only

Neulastim® Pre-filled syringe 6 mg/0.6 ml (10 mg/1 ml)

For subcutaneous administration

COMPOSITION:
Each pre-filled syringe contains:
Pegfilgrastim 6 mg/0.6 ml

For information on the inactive ingredients see section 6 - "Further Information".

- **Read all of this leaflet carefully in its entirety before using this medicine.** This leaflet contains concise information about the medicine. If you have further questions, refer to the doctor, pharmacist or nurse.
- Keep this leaflet. You may need to read it again.
- This medicine has been prescribed for the treatment of your illness. Do not pass it on to others. It may harm them, even if it seems to you that their symptoms of illness are similar.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4 – "Side effects".

Important information for your attention

- If you have been told that you are sensitive to certain types of sugars, consult the doctor before using **Neulastim**.
- **Neulastim** can be self-injected in your home after receiving instruction from a healthcare professional. Please carefully read the instructions for self-injection at the end of this leaflet.
- Following the doctor's instructions (dosage, times of injection and duration of treatment) increases the chances for success of the treatment. In any case, do not discontinue the treatment without consulting the attending doctor. Please read sections 2 and 4 for broader safety information.
- Keep **Neulastim** in the refrigerator (see section 5 - "How should the medicine be stored?").
- The medicine, **Neulastim** pre-filled syringe, is intended for single-use!

1. WHAT IS THE MEDICINE INTENDED FOR?

Neulastim is used to reduce the duration of neutropenia (low white blood cell count) and the occurrence of febrile neutropenia (low white blood cell count with a fever), which can be caused by the use of cytotoxic chemotherapy (medicines that destroy rapidly growing cells), given at intervals of 14 days or more, for malignancy (with the exception of chronic myeloid leukemia [CML] and myelodysplastic syndromes [MDS]).

White blood cells are important as they help your body fight infection. These cells are very sensitive to the effects of chemotherapy, which can cause the number of these cells in your body to decrease. If white blood cells count falls below a certain level, the ability of your body to fight against the bacteria is damaged and you may have an increased risk of infection.

Your doctor has given you **Neulastim** to encourage your bone marrow (part of the bone which makes blood cells) to produce more white blood cells that help your body fight infection.

Therapeutic group
Neulastim is a medicine from the group of proteins called granulocyte-colony stimulating factor (G-CSF).

Neulastim contains the active substance pegfilgrastim. Pegfilgrastim is a protein produced by biotechnology in bacteria called *E. coli*. It belongs to a group of proteins called cytokines, and is very similar to a natural protein (granulocyte-colony stimulating factor = G-CSF) produced by your own body.

2. BEFORE USING THE MEDICINE

x Do not use this medicine if:
you are sensitive (allergic) to pegfilgrastim, filgrastim, *E. coli* derived proteins, or any of the other ingredients of this medicine (listed in section 6 - "Further Information").

! Special warnings regarding use of the medicine
Talk to your doctor, pharmacist or nurse before using **Neulastim**:

- If you experience an allergic reaction including weakness, drop in blood pressure, difficulty breathing, swelling of the face (anaphylaxis), redness and flushing, skin rash and areas of the skin that itch.
- If you have an allergy to latex. The needle cap on the pre-filled syringe contains a derivative of latex and may cause severe allergic reactions.
- If you experience a cough, fever and difficulty breathing. This can be a sign of Acute Respiratory Distress Syndrome (ARDS).
- If you have any of the following or combination of the following side effects:
  swelling or puffiness, which may be associated with passing water less frequently, difficulty breathing, abdominal swelling and feeling of fullness and a general feeling of tiredness. These could be symptoms of a condition called "Capillary Leak Syndrome", which causes blood to leak from the small blood vessels into your body. See section 4 – "Side effects".
- If you get left upper abdominal pain or pain at the tip of your shoulder. This may be a sign of a problem with your spleen (splenomegaly).
- If you have recently had a serious lung infection (pneumonia), fluid in the lungs (pulmonary edema), inflammation of the lungs (interstitial lung disease) or an abnormal chest X-ray (lung infiltration).
- If you are aware of any altered blood cell counts (e.g., increase in white blood cells or anemia) or decreased blood platelet counts, which reduces the ability of your blood to clot (thrombocytopenia). Your doctor may want to monitor you more closely.
- If you have sickle-cell anemia. Your doctor may monitor your condition more closely.
- if you are a patient with breast cancer or lung cancer, **Neulastim** in combination with chemotherapy and/or radiation therapy may increase your risk of a precancerous blood condition called myelodysplastic syndrome (MDS) or a blood cancer called acute myeloid leukemia (AML). Symptoms may include tiredness, fever, and easy bruising or bleeding.
- If you have sudden signs of allergy such as rash, itching or hives on the skin, swelling of the face, lips, tongue or other parts of the body, shortness of breath, wheezing or trouble breathing these could be signs of a severe allergic reaction.
- If you have symptoms of inflammation of aorta (the large blood vessel which transports blood from the heart to the body), this has been reported rarely in cancer patients and healthy donors. The symptoms can include fever, abdominal pain, malaise, back pain and increased inflammatory markers. Tell your doctor if you experience those symptoms.

Your doctor will check your blood and urine regularly as **Neulastim** can harm the tiny filters inside your kidneys (glomerulonephritis).

Severe skin reactions (Stevens-Johnson syndrome) have been reported with the use of **Neulastim**. Stop using **Neulastim** and seek medical attention immediately if you notice any of the symptoms described in section 4 - "Side effects".

You should talk to your doctor about your risks of developing cancers of the blood. If you develop or are likely to develop cancers of the blood, you should not use **Neulastim**, unless instructed by your doctor.

Loss of response to pegfilgrastim
If you experience a loss of response or failure to maintain a response with pegfilgrastim treatment, your doctor will investigate the reasons why, including whether you have developed antibodies which neutralize pegfilgrastim's activity.

Other medicines and Neulastim
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines, including non-prescription medicines and nutritional supplements.

Children and adolescent
There is no information regarding the safety and efficacy of **Neulastim** in children and adolescent.

Pregnancy and breast-feeding
Ask your doctor or pharmacist for advice before taking any medicines.

Neulastim has not been tested in pregnant women.

If you are pregnant, think you may be pregnant or are planning to have a baby, ask your doctor for advice before taking this medicine.

Unless your doctor directs you otherwise, you must stop breast-feeding if you use **Neulastim**.

Driving and using machines
Neulastim has no or negligible effect on the ability to drive or use machines.

Important information about some of the ingredients of the medicine

Neulastim contains sorbitol and sodium

This medicine contains 30 mg sorbitol in each pre-filled syringe which is equivalent to 50 mg/mL.
This medicinal product contains less than 1 mmol sodium (23 mg) per 6 mg dose, that is to say essentially 'sodium-free'.

3. HOW SHOULD YOU USE THE MEDICINE?

Always take this medicine exactly as your doctor has told you. You should check with your doctor or pharmacist if you are unsure.

The dosage and treatment regimen will be determined by the doctor only.

The usual dose is one 6 mg subcutaneous injection (injection under your skin) using a pre-filled syringe and it should be given at least 24 hours after your last dose of chemotherapy at the end of each chemotherapy cycle.

Do not shake **Neulastim** vigorously as this may affect its activity.

Injecting Neulastim yourself
Your doctor may decide that it would be more convenient for you to inject **Neulastim** yourself. Your doctor or nurse will show you how to inject yourself. Do not try to inject yourself if you have not been trained.

For further instructions on how to inject yourself with **Neulastim**, please read the section at the end of this leaflet.

If you accidentally injected a higher dosage of Neulastim
If you use more **Neulastim** than you should contact your doctor, pharmacist or nurse.

If you used an overdose or if a child accidentally swallowed the medicine, refer to the doctor immediately or proceed to a hospital emergency room and bring the package of the medicine with you.

If you forgot to inject Neulastim
If you are injecting yourself and have forgotten your dose of **Neulastim**, you should contact your doctor to discuss when you should inject the next dose.

How can you contribute to the success of the treatment?
Do not take medicines in the dark! Check the label and the dose <u>each time</u> you take medicine.

Wear glasses if you need them.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

4. SIDE EFFECTS

As with any medicine, use of this medicine may cause side effects in some users. Do not be alarmed when reading the list of side effects; you may not experience any of them.

Please tell your doctor immediately if you have any of the following or combination of the following side effects:
- Swelling or puffiness, which may be associated with passing water less frequently, difficulty breathing, abdominal swelling and feeling of fullness, and a general feeling of tiredness. These symptoms generally develop in a rapid fashion.

These could be symptoms of an uncommon (may affect up to 1 in 100 patients) condition called "Capillary Leak Syndrome", which causes blood to leak from the small blood vessels into your body and needs urgent medical attention.

Very common side effects (may affect more than 1 in 10 patients):
- Bone pain. Your doctor will tell you what you can take to ease the bone pain.
- Nausea and headaches.

Common side effects (may affect up to 1 in 10 patients):
- Pain at the site of injection.
- General aches and pains in the joints and muscles.
- Some changes may occur in your blood, but these will be detected by routine blood tests. Your white blood cell count may become high for a short period of time. Your platelet count may become low which might result in bruising.

Uncommon side effects (may affect up to 1 in 100 patients):
- Allergic-type reactions including redness and flushing, skin rash, and raised areas of the skin that itch.
- Serious allergic reactions including anaphylaxis (weakness, drop in blood pressure, difficulty breathing, swelling of the face).
- Increased spleen size.
- Spleen rupture. Some cases of splenic rupture were fatal. It is important that you contact your doctor immediately if you experience pain in the upper left side of the abdomen or left shoulder pain since this may relate to a problem with your spleen.
- Breathing problems. If you have a cough, fever and difficulty breathing, please tell your doctor.
- Sweet's syndrome (plum-colored, raised, painful lesions on the limbs and sometimes the face and neck with fever) has occurred, but other factors may play a role.
- Cutaneous vasculitis (inflammation of the blood vessels in the skin).
- Damage to the tiny filters inside your kidneys (glomerulonephritis).
- Redness at the site of injection.
- Coughing up blood (hemoptysis).
- Blood disorders (myelodysplastic syndrome [MDS] or acute myeloid leukemia [AML]).

Rare side effects (may affect up to 1 in 1,000 patients):
- Inflammation of aorta (the large blood vessel which transports blood from the heart to the body), see section 2 – "Before using the medicine".
- Bleeding from the lung (pulmonary hemorrhage).
- Stevens-Johnson syndrome, which can appear as reddish target-like or circular patches often with central blisters on the trunk, skin peeling, ulcers of mouth, throat, nose, genitals and eyes and can be preceded by fever and flu-like symptoms. Stop using Neulastim if you develop these symptoms and contact your doctor or seek medical attention immediately. See also section 2 – "Before using the medicine".

If a side effects occurs, if one of the side effects worsen, or if you experience a side effect not mentioned in the leaflet, you must consult your doctor.

Reporting of side effects:
Side effects can be reported to the Ministry of Health by clicking on the link "Report Side Effects of Drug Treatment" found on the Ministry of Health homepage **www.health.gov.il** that directs you to the online form for reporting side effects, or by entering the link: **https://sideeffects.health.gov.il**

5. HOW SHOULD THE MEDICINE BE STORED?

Keep this medicine out of the sight and reach of children.

Avoid poisoning! This medicine, and all other medicines, must be stored in a safe place out of the reach of children and/or infants, to avoid poisoning.

Do not induce vomiting unless explicitly instructed to do so by a doctor.

Do not use this medicine after the expiry date which is stated on the carton and on the syringe label after EXP. The expiry date refers to the last day of that month.

Store in a refrigerator (2°C–8°C).

You may take **Neulastim** out of the refrigerator and keep it at room temperature (not above 30 °C) for no longer than 3 days. Once a syringe has been removed from the refrigerator and has reached room temperature (not above 30°C) it must either be used within 3 days or disposed of.

Do not freeze. **Neulastim** may be used if it is accidentally frozen for a single period of less than 24 hours.

Keep the container in the outer carton in order to protect from light.

Do not use this medicine if you notice it is cloudy or there are particles in it.

The medicine, **Neulastim** pre-filled syringe, is intended for single-use only!

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help to protect the environment.

6. FURTHER INFORMATION

In addition to the active substance, the medicine also contains:
Acetate (10 mM), Sorbitol, Polysorbate 20, Water for injection, Sodium hydroxide.
Neulastim is essentially "sodium-free".

How does the medicine look and what are the contents of the package
Neulastim is a solution for injection in a pre-filled syringe (6 mg/0.6 ml).

Each package contains 1 pre-filled syringe and a needle for injection.

The solution is clear and colorless.

Manufacturer: Amgen Europe B.V., Breda, The Netherlands.

Registration holder: Amgen Europe B.V., P.O.B. 53313, Tel-Aviv.

Registration number of the medicine in the National Drug Registry of the Ministry of Health: 133 82 31303

Revised in January 2021 according to MoHs guidelines.

7. INSTRUCTIONS FOR INJECTING WITH THE NEULASTIM PRE-FILLED SYRINGE

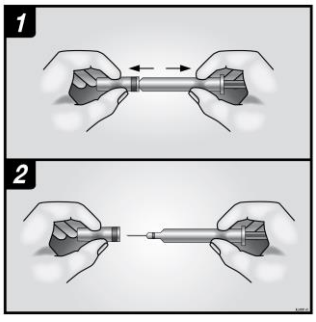
This section contains information on how to give yourself an injection of **Neulastim**. It is important that you do not try to give yourself the injection unless you have received training from your doctor, nurse or pharmacist. If you have questions about how to inject, please ask your doctor, nurse or pharmacist for assistance.

How do you, or the person injecting you, use Neulastim pre-filled syringe?
You will need to give yourself the injection into the tissue just under the skin. This is known as a subcutaneous injection.

Equipment that you need
To give yourself a subcutaneous injection you will need:
- A pre-filled syringe of **Neulastim**
- Alcohol wipes or similar

What should I do before I give myself a subcutaneous injection of Neulastim?
1. Remove from the refrigerator.
2. Do not shake the pre-filled syringe.
3. **Do not** remove the cap from the syringe until you are ready to inject.
4. Check the expiry date on the pre-filled syringe label (EXP). Do not use it if the date has passed the last day of the month shown.
5. Check the appearance of **Neulastim**. It must be a clear and colorless liquid. If there are particles in it, you must not use it.
6. For a more comfortable injection, let the pre-filled syringe stand for 30 minutes to reach room temperature or hold the pre-filled syringe gently in your hand for a few minutes. **Do not** warm **Neulastim** in any other way (for example, do not warm it in a microwave or in hot water).
7. **Wash your hands thoroughly.**
8. Find a comfortable, well-lit, clean surface and put all the equipment you need within reach.

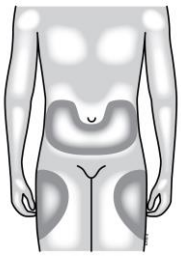
How do I prepare my Neulastim injection?



Before you inject **Neulastim** you must do the following:

1. Hold the syringe barrel and gently take the cap from the needle without twisting. Pull straight as shown in pictures 1 and 2.
   Do not touch the needle or push the plunger.
2. You may notice a small air bubble in the pre-filled syringe. You do not have to remove the air bubble before injecting. Injecting the solution with the air bubble is harmless.
3. You can now use the pre-filled syringe.

Where should I give my injection?



The most suitable places to inject yourself are:
- the top of your thighs; and
- the abdomen, except for the area around the navel.

If someone else is injecting you, they can also use the back of your arms.

How do I give my injection?

1. Clean your skin by using an alcohol wipe.
2. Pinch (without squeezing) the skin using your thumb and forefinger. Insert the needle into the skin.
3. Push the plunger down with a slow constant pressure. Push the plunger all the way down as far as it will go to inject all the liquid.
4. After injecting the liquid, remove the needle and let go of your skin.
5. If you notice a spot of blood at the injection site, dab with a cotton ball or tissues. Do not rub the injection site. If needed, you may cover the injection site with a plaster.
6. Do not use any **Neulastim** that is left in the syringe.

Remember
Only use each syringe for one injection. If you have any problems, please ask your doctor or nurse for help and advice.

Disposing of used syringes
- Do not put the cap back on used needles.
- Keep used syringes out of the sight and reach of children.
- The used syringe should be disposed of in accordance with local requirements. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.